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Hepatocellular carcinoma in HIV positive patients

G. NUNNARI[1,2], M. BERRETTA[3], M.R. PINZONE[1], M. DI ROSA[1], S. BERRETTA[4], G. CUNSOLO[4], M. MALAGUARNERA[5], S. COSENTINO[1], P. DE PAOLI[6], J.M. SCHNELL[2], B. CACOPARDO[1]

[1]Department of Clinical and Molecular Biomedicine, Division of Infectious Diseases, University of Catania, Catania, Italy
[2]Department of Microbiology and Immunology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA
[3]Department of Medical Oncology, National Cancer Institute, Aviano, PN, Italy
[4]Department of Surgery, General Surgery and Senology Unit, University of Catania, Catania, Italy
[5]Department of Biological Chemistry, Medical Chemistry, and Molecular Biology, University of Catania, Italy
[6]Scientific Direction, National Center Institute, Aviano, Pordenone, Italy

Abstract. – Highly active antiretroviral therapy (HAART) has dramatically changed the natural history of HIV-1-infected patients leading to increased survival and a better quality of life. Hepatitis C virus (HCV) and hepatitis B virus (HBV) infections are common among HIV-1-infected subjects and represent the most important risk factors for hepatocellular carcinoma (HCC). Whether HIV plays a direct role in hepatocellular carcinoma (HCC) pathogenesis remains to be established.

HCC clinical course depends on stage of cancer disease, performance status and comorbidities. Therapeutic options include liver transplantation, local antiblastic chemotherapy and biological drugs. In the HIV setting few data are available about treatment options. The increased longevity of patients with HIV imposes new strategies for prevention and therapeutic management of patients. The aim of this article is to provide an up-to-date review of HIV-related HCC in the HAART era.

Key Words:
Hepatocellular carcinoma, HIV, Hepatitis B, Liver transplant, Hepatitis C, Co-infection, HAART.

Introduction

Non-AIDS-Defining Cancers (NADCs)

The advent of highly active antiretroviral therapy (HAART) has dramatically extended the survival rates of patients with human immunodeficiency virus (HIV), leading to suppression even though not eradication of HIV[1-4]. In HIV-infected patients, cancer has become a growing problem, representing the first cause of death[5-7].

HIV has been linked to malignancies since the beginning of its history, in 1981, when Kaposi's sarcoma was reported for the first time[8]. Subsequently, two other malignancies have been related to HIV, being classified as AIDS-defining cancers (ADCs): Non-Hodgkin's lymphoma (NHL) and invasive cervical cancer. In addition, a large number of worldwide studies have shown that HIV infection raises the risk of many non-AIDS-defining cancers (NADCs), including carcinoma of the anus, testis, lung, colon, skin (basal cell skin carcinoma and melanoma), Hodgkin disease and hepatocellular carcinoma (HCC)[9-17].

It is well established that the incidence of ADCs has declined in the HAART era; NADCs, on the contrary, have gradually emerged. Zucchetto et al evaluated the mortality for NADCs among 10,392 Italian patients with AIDS, who were diagnosed between 1999 and 2006, compared with the general population of the same age and sex. NADCs were accounted as the underlying cause of death for 7.4% of HIV-infected patients. The Authors found a 6.6-fold elevated risk of death for NADCs among persons with AIDS, especially due to cancers with viral etiologies: significantly elevated standardized mortality rates (SMRs) were in fact recorded for anal cancer, a human papilloma virus-associated tumor (SMR 270), Hodgkin lymphoma, associated with Epstein Barr virus (SMR 174) and HCC, associated with chronic hepatitis B and C virus infections (SMR 11.1). In absolute terms, the most common

Corresponding Author: Nunnari Giuseppe, MD; e-mail: gnunnari@hotmail.com

cause of death for NADCs was lung cancer (24.6%), followed by liver cancer and Hodgkin lymphoma (both with 11.9%), in accordance with data reported by other Authors[18-21]. The greater risk for infection-related cancers could be further explained by the fact that the altered immune system in HIV-infected persons may reduce its ability to control and suppress the oncongenic viral process. This mechanism is supported by Grulich et al[22] who compared, in a meta-analysis, the cancer risk for HIV positive patients and organ transplant recipients. These populations had a common risk factor for cancer: immunosuppression. Indeed, most of the cancers seen with a higher frequency in both populations had a known infectious cause. The exact role of HIV-induced immunosuppression in the pathogenesis of NADCs remains controversial[23-25]: previous studies failed to associate the increased risk of NADCs with low CD4+ T-lymphocyte cell count[26], some recent studies[27], on the contrary, have shown a significant higher cancer risk for patients with lower CD4+ cell count. Silverberg et al analyzed a cohort of 19,280 HIV patients, followed from 1996 to 2007 and matched for age and sex with 202,303 HIV negative persons. The Authors found that the risk of mouth-throat cancer, anal cancer, colorectal cancer, lung cancer and Hodgkin lymphoma rose as recent CD4+ cell count fell down; after adjusting for other cancer risk factors, including age, smoking status, substance use and viral hepatitis, the risk of NADCs was elevated only among HIV positive persons with a CD4+ count less than 200 cells/mmc, suggesting the importance of earlier HIV detection and treatment.

Longer duration of HIV infection and a history of repeated opportunistic infections are also considered as relevant risk factors for of NADCs. Another possible risk factor for the development of a malignancy among HIV-positive individuals is the use of drugs and medications. In rats, the use of nelfinavir has been shown to be related to the development of thyroid neoplasia[3] but this datum needs a confirmation from human studies.

Focusing on HCC, it is known that the major risk factor is liver cirrhosis and it usually occurs several decades after the initial infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Although it is not known whether HIV infection alone is a risk-factor for HCC (indeed, this has been excluded in large retrospective cohort studies)[29], associated infection with HCV or HBV is common and a significantly increased risk of HCC in the context of chronic viral hepatitis is well-documented. HIV co-infection seems to accelerate disease progression, however, it is unclear whether HIV infection directly increases the likelihood of HCC in viral hepatitis. In addition to potential indirect effects on HCC risk through improvements in immune reconstitution and survival, HAART is known to have some direct hepatotoxic effects, which are amplified among HIV-positive patients chronically infected with HBV or HCV[30]. Nevertheless, just on the basis of the dramatic prolongation of HIV-positive patients' life expectancy, the need of effective prevention strategies against malignancies and the study of their epidemiology, clinical presentation and therapy result mandatory.

HCC: a Rising Problem Among Patients with HIV

Epidemiology and Risk Factors

HCC is the commonest primary cancer of the liver[31] and, according to the WHO report[32], the fourth commonest cause of death. The estimated incidence of new cases worldwide is about 500,000-1,000,000 per year, causing 600,000 deaths globally per year[33]. Although there are large areas of the world where the incidence of HCC is still unknown[34-36], several countries like East Asia and some Sub-Saharan African regions result to be affected by a very high prevalence of HCC (over 20 cases/100,000 population)[4]. Areas with moderately high risk (11-20 cases/100,000 population) include Italy, Spain and Latin America; France, Germany and the United Kingdom have instead an intermediate risk (5-10 cases/100,000 population). A relatively low prevalence (less than 5 cases/100,000 population) is found in United States, Canada and Scandinavia. The incidence of HCC has been rising in developed western countries in the last two decades[4-37], along with the emergence of hepatitis C virus infection and to the rise of immigration rates from HBV-endemic countries. In addition, even though the incidence of HCC reaches its highest peak among persons over 65 years[38], an increased incidence among younger individuals has been noted in the last two decades both in USA and Europe.

In HIV positive patients HCC prevalence rate is higher with respect to the population average (82/10,000 according to the Data Collection on Adverse Events of Anti HIV Drugs), being HCV

infection the strongest predictor for liver related death, followed by HBV[39]; this observation was confirmed by many studies: a large retrospective cohort study on US veterans demonstrated that HIV positive persons had a higher risk to develop HCC than HIV negative ones but, after adjusting for HCV and alcohol abuse, HIV status was not independently associated with cancer[40]. The 2001 French Mortavic study[41], a prospective 1-year cohort study involving 25,178 HIV positive patients, showed a significant increase in death from end-stage liver disease (ESLD) and HCC, when 2001 data to those coming from similar cohorts collected in 1995 and 1997. Death due to ESLD rose from 1,5% to 14.3% whereas HCC-related mortality rose 5-fold, from 4.7% to 25%; interestingly, all deaths from HCC were in patients with HCV co-infection. Throughout the same period, AIDS-related mortality rate fell from 91.6% (in 1995) to 48.7%, suggesting that the increased longevity in the HAART era could be a reason for the increased HCC rate in the 2001 cohort. In a prospectively followed cohort of HIV-infected individuals, HCC deaths related to HCV infection raised from 10% in 2000 to 25% in 2005[5]. On the contrary, the incidence of HCC development and related deaths among HIV-HBV co-infected individuals seemed to be stable[5]. A retrospective study conducted on a cohort of US veterans with hepatitis C between 1991 and 2000[43] showed that the incidence of HCC did not differ between HIV/HCV co-infected and HCV mono-infected patients in the HAART era, whereas it was significantly lower among HIV/HCV co-infected individuals previously to HAART introduction. This datum supports the premise that, in the pre-HAART-era, HIV patients did not survive enough to develop HCC. Similar conclusions rose from other retrospective studies examining cohorts from countries where HAART is largely unavailable, which found the incidence of HCC to be lower or equal to average population rates[44,45]. In 2004, the Italian Cooperative Group on AIDS and Tumors (GICAT)[46], while collecting data on malignancies occurring in HIV patients since 1986, identified a total of 41 consecutive patients with HCC (from a joint Italian and Spanish database) and retrospectively investigated the main epidemiological characteristics of these patients comparing them with those of a 384 HIV negative control group, diagnosed over the same period. The GICAT study emphasized the younger age of HIV positive patients at the diagnosis of HCC (age 40-46 vs. 60-70 in HIV negatives). In most studies HCV infection was the main risk factor for HCC development in both HIV positive and negative subjects. The median time to develop HCC after HCV infection was found to be around 22 years in HIV positive patients: 10 years shorter than that reported among HIV negative patients that acquired HCV infection with transfusion[7]. Alcohol abuse (which is often associated with HIV risk behaviors) and insulin resistance (which causes non alcoholic fatty liver disease and frequently occurs in HIV-infected individuals submitted to protease inhibitors) are other potential risk factors for HCC development among HIV-positive patients[48,49].

HIV-HBV and HIV-HCV Co-Infection: Prevalence and Significance of a Complex Interaction

Co-infection with HCV and/or HBV is common among HIV-infected persons, because of shared routes of transmission, although the prevalence of co-infection varies markedly according to the geographic origin and demographic characteristics of infected patients[50].

Approximately 25% of HIV positive persons in the Western world has HCV co-infection[51]; the European SIDA cohort, by examining 3,048 HIV positive patients, noticed that the prevalence of HIV/HCV co-infection rose from 33% to 75% when considering intravenous drug users (IVDUs)[52]. In the USA, the highest rates of HIV/HCV co-infection were also seen among IVDUs[53]. As refers to HBV, up to 9% of HIV positive patients in Europe are HBsAg positive[54,55]. In Italy, between 3% and 4% of HIV infected individuals are chronic carriers of HBsAg[56]. The recorded prevalence is likely to be inaccurate, because of the large number of patients with occult HBV infection, associated to detectable HBV DNA on quantitative polymerase chain reaction (PCR)[57,58].

HCV usually leads to the development of HCC through the stage of cirrhosis, which can take 28-30 years to occur[59,60]. Cirrhosis is almost a prerequisite for the development of HCV-related HCC: HCV is not able to integrate into the host genome and the major hypothesis to explain hepatocarcinogenesis in patients with HCV is related to immune-mediated inflammation and hepatocellular injury. HBV chronic infection is another major cause of HCC[61] but, differently from HCV, HCC may occur in HBsAg carriers without cirrhosis, because of the direct involvement of a

number of viral-related factors (viral proteins, BCP mutation in the viral genome, Pre-S deletion mutants)[61,62]. Furthermore, HBV can integrate its DNA into the host genome, with several mutagenic consequences, including large inverted duplications, deletions, amplifications and traslocation, resulting in chromosomal instability[66-68]. As expected, patients with HCV-HBV co-infection have a higher risk of developing HCC than those mono-infected: for this reason, vaccination against HBV infection should be proposed to all patients with chronic hepatitis C[65].

The role of HIV on cancer has long been investigated. In vivo studies on murine models have shown a potential role of the HIV Tat gene in liver tumorigenesis[66-68]. In transgenic mice expressing this gene, a greater incidence of hepatocellular carcinoma and other extra-hepatic malignancies has been found, thus emphasizing that the potential oncogenic effect of Tat gene is not liver-specific. Tat seems to be able to stimulate cell proliferation, because of its anti-apoptotic activity[69,70], angiogenic functions[71,72] and ability to induce expression of growth factors[73], cytokines[74,75] and transcription factors[76]. This experimental datum is in contrast with a number of epidemiological studies denying any particular role of HIV itself on HCC development: a large retrospective study by Giordano et al[29], for instance, showed that HCC rate was not higher in HIV mono-infected patients than in general population. Anyway, even though HIV itself might seem not able to cause HCC, there is a clear evidence that HIV could accelerate the progression of HCV- and HBV-liver disease to cirrhosis and HCC. In fact, the presence of HIV alters the natural history of HCV infection: it increases the likelihood of chronicity (over 90%) due to the lack of critical CD4+ T-cell responses against HCV[77,78]. Furthermore, once chronic HCV infection is established, liver disease progression is much faster, resulting in a higher frequency of cirrhosis and its complications compared to HCV mono-infected patients[79-82].

The molecular mechanisms of accelerated fibrosis in co-infected patients are not fully understood: an attempt was made by Galastri et al[10], who studied HIV-gp120 capability to exert multiple effects on human hepatic stellate cells (HSCs), modulating their phenotype in a profibrogenic way. Incubation of HSCs with gp120 significantly increased HSCs migration and expression of proinflammatory cytokines, including monocyte chemoattractant protein-1 (MCP-1) and type 1 procollagen. Recent data suggest that HIV gp-120 binding to CXCR4 receptor, expressed on the surface of hepatocytes and HSCs, is able to upregulate tumor necrosis factor (TNF)-related apoptosis, inducing ligand (TRAIL) R2 expression. According to the Authors, HIV infection makes hepatocytes more susceptible to liver injury[84].

During HIV co-infection, increased liver damage may also be mediated indirectly by antiretroviral drugs hepatotoxicity and by immune reconstitution syndrome[5].

Further prospective studies are needed to better evaluate the HIV role in co-infected subjects with HCC. It would be worthy to avoid common bias, which appear recurrent in some of the above mentioned retrospective cohort studies: for instance, not all HCV-HBV patients had been tested for HIV, thus implying the possibility to underestimate the prevalence of co-infected persons; furthermore, since time of viral hepatitis infection is often missing, it might be difficult to correlate HCC rates to mono- or co-infection. In fact, patients with isolated HCV or HBV may just have acquired infection earlier than co-infected patients and this different period of exposure to viral insult may obviously influence HCC incidence. Considering these evaluations, keypoints of an ideal prospective study should be: cross-testing for co-infections before individual allocation to groups, standardized screening for HCC and regular evaluation of HIV viral load in the co-infected cohort, in order to evaluate the potential effect of HAART-induced viral suppression on HCC pathogenesis.

Clinical Characteristics

During its initial stage, HCC is generally asymptomatic in all patients, then, in more advanced phases, hepatomegaly, jaundice and abdominal pain may appear. However, HCC clinical presentation and prognosis considerably vary according to the number and size of tumoral lesions. Liver cancer may appear either as a single nodular or infiltrating lesion with an eccentric growth or as a multinodular widespread tumor *ab initio*. In some patients HCC lesions have a slow growth rate, with a two-fold increase in 20 months, in other cases it can double within less than one month[86-88]. Multinodular HCC is more often found in patients with more than one risk factor[89] and needs to be classified in primitive multicentric HCC or metastatic cancer from a primitive HCC. This distinction has important clinical implications because primitive multicen-

tric HCC are less aggressive and recur less frequently after ablation than metastatic cancers from a primitive HCC[90,91].

Among HIV positive patients cumulative clinical data suggest a more aggressive course of HCC[92-95]. Patients with HIV from the HIV-HCC Italo-Spanish Group[6] showed a more advanced and infiltrating HCC (also with extranodal metastases), a more advanced stage of cirrhosis at presentation and a reduced survival rate in comparison with HIV negative patients. A 2007 U.S.-Canadian multicenter retrospective study[96] identified 63 HIV-infected patients affected by HCC from 1992 to 2005 and compared them to 226 HIV-negative HCC patients. Patients with HIV not only were younger and more frequently symptomatic than HIV-negative patients but also showed higher median alfa-fetoprotein levels. In contrast with other studies, in this case tumor staging and survival were similar between case and controls. In untreated HCC cases, the presence of undetectable HIV-RNA was an independent predictor of a better survival. In a recent, large, multicenter, observational study, Berretta et al[97] confirmed HIV-positive HCC subjects to be younger and to have a shorter survival time after treatment than HIV-negative patients.

HCC: Treatment Options

HCC treatment is usually classified as curative or palliative. Curative treatments are represented by surgical resection, orthotopic liver transplantation (OLT) and local ablative therapies, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA)[98-99]. Surgical resection is the treatment of choice in solitary tumors less than 5 cm in diameter, without vascular invasion or extrahepatic spread, with preserved hepatic function and absence of portal hypertension, assuring a 5-year survival rate of 50%[100,101]. OLT is, instead, the best option for cirrhotic patients with a single tumoral lesion less than 5 cm in diameter that are not candidate to resection and when there are up to 3 lesions smaller than 3 cm, without vascular invasion or metastasis, according to the Milan criteria. In these cases the 5-year survival rate overcomes 70%[102]. In patients that are not eligible for resection or transplantation, owing to comorbidities, liver disfunction or limited surgical resources, PEI and RFA are a potential treatment for small tumors, usually less than 3 cm in size; for early-stage HCC, RFA has been seen to induce a complete response in about 80% of patients, with a 5-year survival of 50% and recurrence rates comparable to surgical resection[103].

Unfortunately, most patients with HCC have advanced disease at diagnosis. They are candidates for palliative treatments, that include transarterial chemoembolization (TACE), chemotherapy, hormonal compounds and immunotherapy[105]. TACE has been shown to improve survival when applied to carefully selectioned patients[106,107]. It is indicate for unresectable multinodular HCC, without vascular invasion and extrahepatic spread.

To date, with systemic chemotherapy, durable remission has rarely been reported and no significant survival benefits have been conclusively demonstrated, probably because of poor chemosensivity of HCC cells[105,108]. More recently, sorafenib (an oral multikinase inhibitor of the vascular endothelial growth factor receptor) resulted better than placebo in prolonging median survival time as well as time to radiologic progression in patients with advanced HCC[109] and it has been approved for advanced disease. Molecularly targeted therapy seems a new option for patients not amenable to resection or transplant; despite the clinical relevance of HCC in HIV-HBV/HIV-HCV co-infected patients, only two case reports have been published about its successful use in patients with HIV and its coadministration with HAART[110,111]. Other antiangiogenic therapies in clinical development are sutinib[112] and the combination of bevacizumab and erlotinib[113], but no data are available at the moment about patients with HIV. Mammalian target of rapamycin (mTOR) inhibitors have shown activity in small cohorts of patients with HCC[114], but these data need to be validated in clinical trials to understand if they could represent a therapeutic chance for persons with unresectable cancer and, in particular, for patients with HIV. Presence of sexual hormones receptors in HCC cells has suggested the possibility to use antiestrogens like tamoxifen in non-surgical HCC, but several trials failed to demonstrate benefits in terms of response or survival in advanced HCC treated with tamoxifen[115-118].

HCC in patients with HIV is often advanced at presentation, not allowing curative therapeutic strategies. Until a few years ago, HIV infection was an exclusion criteria for liver transplantation. The main concern was the risk of HIV progression after OLT, a poor post-transplantation prognosis and eventually a waste of graft[119]. Ettorre et al[120] showed that almost half of HIV-positive pa-

tients affected with HCC were not suitable for surgical treatment and comprehensively only 28% of them had the opportunity to receive a successful surgical treatment.

The GICAT cohort reported that in a series of 41 HIV positive patients affected by HCC, 15 (35%) of them fulfilled the Milan criteria and could potentially have been treated with OLT as a curative intent, but actually none of them underwent liver transplantation and only two underwent surgical resection with a 2-year survival of 41% in treated patients and 0% in untreated cases[6].

Since the introduction of HAART, the outcome of HIV infection has dramatically changed. Patients with HIV have a better long-term survival; as a consequence, liver transplantation needs to be considered to treat HCC. Several studies found that most HIV positive transplanted patients have a good long-term survival[121,122]. A 2008 report of Di Benedetto et al[122] showed a series of 7 HIV positive patients with HCC that, by fulfilling the Milan criteria, underwent OLT. After a mean follow up of 232 days, the overall survival rate was 85.7% and only one patient died of a myocardial infarction with a functioning graft and no HCC recurrence. Radecke et al reported that out of 5 cases of OLT in HIV-infected cirrhotic subjects, two had stable liver function and non-progressive HIV infection under HAART, 61 and 23 months after OLT, respectively; unfortunately, in this report, three out of five patients died due to graft failure.

Clinical post-transplant management of OLT in HIV positive patients is doubtless more complex than in the HIV negative counterpart. The main reported problem in these patients has been an earlier and more aggressive HCV recurrence (experienced in about 33% of patients)[123], fast occurrence of hepatic fibrosis, a greater rate of rejection (from 33% to 38%)[121-124] and a higher incidence of tacrolimus toxicity[125].

The outcome of HIV-positive liver recipients depends on the immunological status of the patient at the time of OLT[126]. There is a considerable agreement about the necessity of a full virological control of the underlying HIV infection before OLT: in fact, transplanted patients with higher CD4+ cell count and undetectable HIV viral load display clinical courses similar to HIV negative recipients. Di Benedetto et al proposed some criteria to select HIV positive patients with HCC eligible to OLT: firstly, patients must completely fulfill the Milan criteria, they should also have an undetectable HIV viral load (< 50 copies/mL) and a CD4+ cell count more than 200/mmc. Secondly, after OLT, HAART needs to be reinstituted as soon as clinically possible according to the opinion of a multidisciplinary transplant team (surgeons, infectivologists and oncologists) with great experience in the management of pharmacologic interactions between HAART and immunosuppressive agents (see also Table I).

In conclusion, the latest evidence suggests that OLT should be considered as a real opportunity for patients with HIV and HCC: even if accurate selection protocols are obviously essential, with regards to HIV status and HCC stage, nowadays the key question is not anymore if, but who should be referred to liver transplantation.

HCC: Primary, Secondary and Tertiary Prevention

Prevention and early diagnosis are key points to the management of HCC, but, at present, there are no universal guidelines, especially when it occurs in HIV-positive patients *(*see also Table II*)*. Primary prevention in subjects with HIV should entail efforts to promote alcohol avoidance and strongly recommend vaccination against HBV. HCC has been the first human cancer amenable to prevention using mass vaccination programmes.

Secondary prevention should include regular exams aimed at early detection of HCC. The European Association for the Study of the Liver (EASL) has proposed guidelines describing patient selection and surveillance intervals for HCC screening in HIV-HCV and HIV-HBV co-infected individuals. Six-monthly ultrasonography and alpha-fetoprotein (AFP) levels measurement are the two most commonly used methods to screen cirrhotic patients for HCC. The use of AFP alone for early diagnosis of HCC in HIV co-infected patients[118] is not recommended and may be suggested only where and if ultrasonography is unavailable. In fact, even though AFP values higher than 400 ng/ml are usually considered as diagnostic of HCC, it should be reminded the possibility of false-positive results with AFP, since HAART has been shown to induce a substantial increase of AFP levels[129]. The GICAT group, by noting a more advanced HCC at diagnosis in HIV positive patients, apparently unrelated to a true delay in diagnosis, suggested to shorten the interval for HCC screening considering that hepatocarcinogenesis could be a more rapid process in HIV positive cirrhotic sub-

Table I. Criteria for considering liver transplantation in HIV-infected patients (according to Di Benedetto 2008 and O'Grady 2005).

Liver disease criteria
- Child-Turcotte-Pugh score ≥ B7; MELD score ≥ 14

*Milan criteria: **
- No more than 3 tumour nodules
- No nodule greater than 5 cm in diameter
- Absence of macroscopic portal vein invasion
- Absence of recognizable extrahepatic disease

HIV infection criteria

Immunological criteria
- None of AIDS-defining opportunistic infections in the previous year
- CD4 cell count > 200 cells/μL or > 100/μL in case of therapy intolerance

Virological criteria
- Undetectable HIV viral load (< 50 copies/mL) in the last 12 months or effective therapeutic options for HIV infection during the post-transplant period

General criteria
- Favourable psychiatric evaluation
- Social stability
- No alcohol abuse for at least six months
- No drug consumption for at least two years (patients who are on stable methadone maintenance programmes can be included and can continue on the maintenance programme after the procedure)
- No extrahepatic malignancy
- No pregnancy

*Patients with HCC who are being considered for liver transplantation should not have a needle biopsy due to the significant rate of needle-track seeding leading to post-transplant recurrence.

jects[6]. Another aspect dealing with secondary HCC prevention in patients with HIV consists in treating HCV and HBV co-infection. Treatment with interferon alpha and ribavirin may induce a persistent negativization of HCV viremia in 27-40% of HIV-HCV co-infected individuals and seems to reduce the risk of HCC in these cases[130]. Moreover, HCV eradication in HIV co-infected patients results in a definitive improvement of liver function and it seems to ameliorate tolerance to antiretroviral agents[31]. In particular, therapy with pegylated-IFN alpha plus ribavirin appears able to slow down the rate of liver disease progression, although the likelihood of achieving a sustained virological response (SVR) is lower in co-infected persons than in those with HCV mono-infection[132-137]: nevertheless, 48 weeks of ribavirin and pegylated-interferon alpha therapy at doses used for HCV mono-infected patients seems to be advisable[138]. Unfortunately HCV therapy in HIV patients is affected by several safety concerns: more severe and frequent mielosuppression, more frequent anemia (particularly due to ribavirin-zidovudine interaction), increased risk of lactic acidosis and a poorer response in those cases with low CD4+ cell count[139-144]. HBV treatment also appears to substantially reduce HCC incidence in patients with severe cirrhosis[145] and there are reasons to suspect the same effect in HIV co-infected patients. Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred[146].

Table II. HCC prevention.

Primary prevention
- Alcohol avoidance
- Injection drugs avoidance
- Vaccination against hepatitis B

Secondary prevention
- 6-monthly ultrasonography + AFP
- Treatment of HCV and/ or HBV co-infection

Tertiary prevention
- No significant options

Finally, as far as we know, no relevant data on tertiary prevention (which aims to reduce HCC recurrence after resection) are available for HIV-positive individuals. Moreover, also cancer related fatigue could be studied in this particular setting of patients[147].

Conclusions

Currently, in areas where HAART is available, a rapid increase of HCC prevalence is occurring among HIV-positive individuals. It is reasonable to hypothesize that, in a few years, this could involve developing countries too. Considering the more aggressive clinical behaviour and progression of HCC in co-infected patients, there is a need for effective screening techniques, prevention programs and specific management guidelines. Large, multicentre, randomized clinical trials are urgently needed, in order to better define the criteria for surveillance and the effect of early diagnosis on outcome. In addition, important needs for future research include a further evaluation of the feasibility of liver transplantation and efficacy of new therapeutic agents.

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